REMARKS

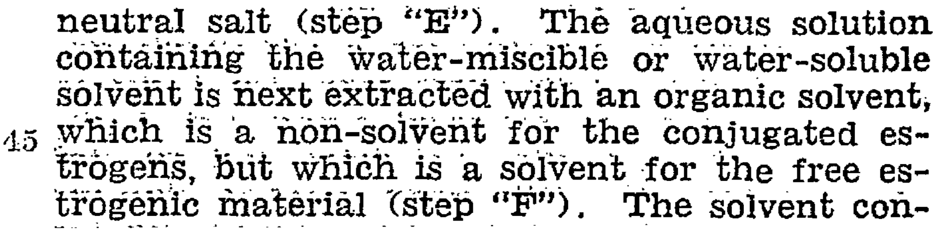
Favorable consideration and allowance are respectfully requested for claims 1, 2, 5, 6, and 8 – 19 in view of the foregoing amendments and following remarks.

The rejections of claims 1, 2, 5, 6, 7 – 18 under 35 U.S.C. § 103(a) over Turner et al. (2,519,516) in view of Wang et al. (WO 01/27134) as supported by Klaassen et al. (Casarett and Doull's Toxicology, April 2001) and Hurst et al. (Methods of Analysis for Functional Foods and Nutraceuticals, 2002) and for certain claims, further in view of the Merck Index and Neeb et al. and for certain claims, further in view of Fishman and Nendza, are respectfully traversed.

Claim 1 is amended to clarify that the liquid-liquid extraction involves extracting the non-conjugated lipophilic compounds.

Turner relates to a serial extraction process where a number of different liquid-liquid extractions are performed to ultimately recover estrogenic materials. In Turner, the conjugated and nonconjugated (free) estrogens are separately recovered. First, pregnant mare urine is concentrated (step B). Then estrogens (both free and conjugated) are removed by extracting with a water soluble or water miscible organic solvent (step C) and the solvent extract is concentrated (step D). At this point the estrogens are in the organic solvent. This solvent extract is then diluted with water and another extraction is performed, with a solvent that is selective for free estrogenic material but is a nonsolvent for the conjugated estrogens (step F). The aqueous fraction containing the conjugated estrogens is then extracted with a solvent for the conjugated estrogens (step G). Further processing steps are then required to ultimately obtain the conjugated estrogen precipitate.

Thus, step F starts with conjugated estrogens in an organic water-soluble or water-miscible solvent (methanol – a solvent for both free and conjugated estrogens). Water is added, and a solvent selective for nonconjugated estrogens is added for an extraction (benzene, which is highly nonpolar). Directly thereafter, in step G, a solvent for the conjugated estrogens is added which has a limited solubility with water (butanol). The Office Action argues that the following disclosure in column 4 of Turner amounts to an extraction of conjugated estrogens where they are partitioned into the aqueous phase:



> neutral salt (step "E"). The aqueous solution containing the water-miscible or water-soluble solvent is next extracted with an organic solvent, which is a non-solvent for the conjugated estrogens, but which is a solvent for the free estrogenic material (step "F"). The solvent con-

Wang relates to a process where salt is added "to lower the solubility of conjugated estrogens in an aqueous phase, and . . . liquid-liquid extraction [partitions] the majority of conjugated estrogens into the organic phase", see page 2, lines 24-26. Thus, Wang is directed to partitioning conjugated estrogens into the organic phase of an extraction. Wang provides no teaching regarding separating non-conjugated estrogens or phytoestrogens. Wang provides no information as to whether or not conjugated estrogens may be successfully recovered from the *aqueous* phase in the absence of salt. In Table 1, on page 6, Wang indicates that in the absence of salt, the recovery rate of conjugated estrogens from the organic phase was 18 %. Wang does not provide any indication as to what the recovery might be from the aqueous phase.

The other 18 data points provided in Table 1 of Wang all relate to extractions including salt. Because the goal of Wang is to obtain purified conjugated estrogens from pregnant mare urine and omitting salt would not effectively facilitate separating the conjugated estrogens from the pregnant mare urine, Wang teaches away from salt-free extractions partitioning conjugated estrogens into the aqueous phase.

Moreover, one of skill in the art would have no reason to try such a salt-free extraction based on Wang, because Wang is directed to removing conjugated estrogens from pregnant mare urine, see the section entitled "Summary of the Invention" on page 2. If no salt is added, one of skill in the art would understand from Wang that the conjugated estrogens are not effectively extracted and the method would fail to achieve the purpose of separating the conjugated estrogens from the pregnant mare urine. As such, not only does Wang teach away from a salt-free extraction, one of skill in the art would have no reason, based on Wang, to perform a salt-free extraction.

Moreover, Wang provides no indication as to the purity of the conjugated estrogens that may be recovered according to the methods described therein. Absent some showing that the conjugated estrogens may be recovered from the aqueous phase at a useful purity level, one of skill in the art would not even consider the teachings of the reference.

The combination of Wang and Turner is improper because no matter how it is done, a basic requirement of one of the references cannot be achieved. Turner calls for an extraction partitioning conjugated estrogens into the aqueous phase (step F). In a later step, Turner calls for an extraction partitioning conjugated estrogens into the organic phase (step G). Wang, on the other hand, is directed to salt based extractions partitioning conjugated estrogens into the solvent phase. A person of skill in the art reviewing Turner would not look to Wang because Wang teaches away from extractions partitioning conjugated estrogens into the aqueous phase. Even if one were to try to combine the teachings of Wang with Turner, the result would require defeating the purpose of one of the references, namely Turner's requirement that the conjugated estrogens be in the aqueous phase or Wang's teaching to partition the conjugated estrogens into the solvent phase.

If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, a proper showing of obviousness has not been made. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). The MPEP, at section 2143.01 includes two sections addressing improper obviousness rejections, one titled "V. The Proposed Modification Cannot Render The Prior Art Unsatisfactory For Its Intended Purpose" and the other "VI. The Proposed Modification Cannot Change The Principle Of Operation Of A Reference". Each of these canons of obviousness jurisprudence is raised by the proposed combination and modifications of the references. In particular, modifying Wang's general teaching of adding salt by *not adding salt* defeats the purpose of the extraction and prevents the Wang method from effectively achieving the goal of extracting conjugated estrogens *away from* the pregnant mare urine (aqueous phase). Since not adding salt defeats the whole point of the Wang extraction, there can be no doubt that the proposal to disregard the teachings of Wang and not add salt changes the principle operation of the Wang reference.

Moreover, there is nothing that would provide one of skill in the art with an expectation of success in ignoring the express teaching of Wang to add salt and partition the conjugated estrogens into the solvent phase of the extraction. Indeed, given Wang's focused instructions to add salt and partition conjugated estrogens from the solvent phase, one of skill in the art would not expect that it would be easy to recovery satisfactory amounts of conjugated estrogens from the aqueous phase. As described in the specification of the present application, there are a number of problems commonly associated with liquid-liquid extractions including vigorous foaming, sedimentation, emulsification and poor phase separation. Further complicating liquid-liquid extractions of pregnant mare urine (PMU) is the wide variability in the composition of PMU which renders extraction processes unpredictable. Given these complexities and the complete absence of any discussion by Wang of success in partitioning conjugated estrogens into the aqueous phase or any discussion of the purity levels achieved by Wang, a person of skill in the art would have no expectation of success in the proposed combination.

Yet another reason that the proposed combination of Turner and Wang is improper regards the particular solvents described in the references. Assuming, arguendo, that one of skill in the art were to try to combine the teachings of Wang and Turner, the result would be that the solvent used in the later extraction (step G) (butanol in the example) would be substituted by the ethyl acetate of Wang. This is because these two solvents are more comparable than are ethyl acetate and benzene and because the butanol and the ethyl acetate are used in a similar process, to partition the conjugated estrogens into the organic phase. A chart comparing the properties of these solvents is attached as Appendix A and shows that butanol and ethyl acetate are chemically more similar than benzene and ethyl acetate (consider, in particular, the water solubility and partition coefficients).

The presently claimed methods do not require the addition of salt. Indeed, when salt is added, the claimed method cannot be achieved, because the conjugated estrogens solubilize in the solvent. Because Wang requires salt for effectiveness and teaches away from a salt-free extraction and because Turner generally encourages the addition of salt, the result of any combination of Wang and Turner would always result in a method including the step of adding salt. Absent the present claims as a roadmap, the skilled artisan would not have reached the present invention, where purified conjugated estrogens are recovered from the aqueous phase.

Further, the aim of the present invention is neither the separate recovery of free estrogenic material nor the extraction of conjugated estrogens from PMU by liquid-liquid extraction. Instead, the claims are directed to the removal of undesired non-conjugated lipophilic compounds, in particular those derived from the ingested plants (e.g. non-conjugated flavonoids, non-conjugated isoflavonoids, and non-conjugated norisoprenoids - often also called "phytoestrogens") and therefore provides an additional purification step for extracts already enriched with regard to the conjugated estrogen fraction. As a result, one of skill in the art would not be inclined to consider reference relating to extracting estrogens from PMU.

As explained above, the combination of Turner, Wang, Klassen and Hurst fail to obviate claim 1. The remaining claims are all dependent either directly or indirectly, from claim 1. The additionally cited references, the Merck Index and Neeb, or Fishman and Nendza, do not make up for the deficiencies of the previously-cited four references. With regard to claims 11 -12 (limitations towards the pH value) and claims 15 -18 (limitations towards the volume ratio), the teachings of Wang are directed to a different process (i.e., the extraction of conjugated estrogens from PMU with ethyl acetate after addition of salt) and cannot simply be imposed on a different process (i.e., the removal (extraction) of non-conjugated phytoestrogens from PMU with ethyl acetate without addition of salt) as provided in the present claims.

Thus, the references cannot be properly combined as suggested in the Office Action. If they are combined, either the essential purpose of the reference is destroyed, or the combination fails to meet every limitation of claim 1. Accordingly, reconsideration and withdrawal of these rejections are respectfully requested.

The rejection of claim 19 as obvious over the proposed combination of nine different references: Turner, et al., Wang, et al., Klaassen, et al., Hurst, et al., the Merck Index, Neeb et al., together with Ban U.S. 5,723,454, Grotewold, et al., and Dakashini, et al., is respectfully traversed.

Claim 19 depends from claim 6 and is allowable for at least the same reasons claim 6 is allowable, as discussed above. Claim 19 adds that the depletion of phenolic urine contents is obtained by solid-phase extraction (SPE) on a non-ionic semipolar resin or on a hydrophobized silica gel.

At the outset, Applicant's wish to point out that the sheer number of references relied on for this rejection suggest a hindsight piecing together of claim elements and that the propriety of the obviousness rejection is questionable. The Office Action offers Ban as making up for the failure of the other 8 references to describe the claimed invention. The Office Action admits that Ban is silent as to the fate of the flavonoids in the SPE column. Indeed, it is not clear where the flavonoids would be following the process of Ban. One of skill in the art might reasonably expect that flavonoids would not remain on the column through an aqueous wash.

As such, one of skill in the art would have no reasonable expectation of success in the proposed combination. Accordingly, the obviousness rejection cannot be properly maintained and reconsideration and withdrawal thereof are respectfully requested.

A document complying with the request for copies of claims of all copending U.S. applications which set forth similar subject matter to the present claims is being prepared and is forthcoming.

CONCLUSION

In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket No. 029300.52141US).

Respectfully submitted,

May 22, 2007

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Appendix A

Property	**Benzene**	**Butanol**	**Ethyl Acetate**
Physical state	Rhombic prisms	refractive liquid	liquid
Melting point	5.5°C	-90°C	−83.6 °C
Boiling point	80.1°C	117-118°C	77.1 °C
Density	at 15°C, g/cm3 0.8787	d20/4°C, 0.810	0.897 g/cm^3 (25°C)
Solubility: Water at 25°C Organic solvents	< 0.2 mL /100 mL Alcohol, chloroform, ether, carbon disulfide, acetone, oils, carbon, tetrachloride, glacial acetic acid	7.8 mL/100 mL	8.0 g/100 mL ethanol, acetone, diethylether, benzene
Partition coefficient: Log KOW*	2.89	0.88	0.73
Vapor pressure	75 mm Hg at 20°C	7.00 mm Hg @ 25°C	73 mm Hg (20°C)
Henry's law constant at 25°C	5.5x10-3 atm-m3 /mol	8.81 x 10-6 atm-m3/mole	1.38 x 10-4 atm-m3 /mol
Autoignition temperature	498 °C		427 °C
Flashpoint	27°C (closed cup)	36-38°C (closed cup)	-3.3°C (closed cup)
Conversion factors	1 ppm = 3.24 mg/m3 at 20 °C and 1 atm pressure; 1 mg/m3 = 0.31 ppm	1 mg/m3 ÷ 0.33 ppm at 20°C 1 ppm ÷ 3.03 mg/m3 at 20°C	
Explosive limits	1.3% (lower limit); 7.1% (upper limit)		Lower: 2.2 % Upper: 11.5 %

* octanol/water partition coefficients

Data taken from Sigma-Aldrich and Wikipedia